IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#13
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5/21/02

In re Application of	)	
	)	
ANDREW J. DANNENBERG	)	Group Art Unit: 1617
	)	
Patent Application No. 09/554,604	)	Examiner: S. Wang
	)	
Filed: May 31, 2000	)	
	)	
For: CYCLOOXYGENASE-2 INHIBITION	)	

RESPONSE TO FINAL ACTION AND TO
THE ADVISORY ACTION OF MAY 1, 1002

Honorable Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

This is further in response to the final Office Action of March 15, 2002 and to the advisory action of May 1, 2002.

Please amend the above-identified application as follows:

IN THE CLAIMS

The amendments made in the response of April 16, 2002,.are repeated.

Remarks

In view of the above, on entry of said amendments, Claims 3-5, 7, 9, 10, 11 and 17 will be in the case.

In view of the above, the only issue is whether Claims 3-5 and 17 are patentable over Gregory et al U.S. Patent No. 6,172,096 in view of Talley U.S. Patent No. 5,643,933. The office action takes the position that even though Gregory does not expressly teach the treatment of the

liver diseases listed in claim 3, it would have been *prima facie* obvious to a person of ordinary skill in the art to employ the specified compounds for treating hepatitis disease because these compounds are known generally to be useful for treating inflammatory diseases (Talley) and are known to be useful to treat liver related diseases (Gregory et al).

Reconsideration is requested.

The starting point is the FDA's conclusion in 1982 described in previous submissions, that hepatotoxicity is a class characteristic of NSAIDs (non-selective inhibitors of both cyclooxygenase-1 and cyclooxygenase-2).

It is submitted that the discovery herein that there is a net benefit to administering selective inhibitors of cyclooxygenase-2 to those with liver diseases as claimed (chronic viral hepatitis B, chronic viral hepatitis C, alcoholic liver injury and nonalcoholic steatohepatitis), is unobvious. It is submitted further that while the applied prior art (Gregory) may teach a net benefit for treatment in respect to transplant rejection and autoimmune diseases, even though liver related, there is no such teaching in the prior art in respect to the diseases treated in the claims, and it is submitted that there would therefore be no reasonable expectation of success from the prior art in the case of the claimed methods.

The office action in response to the above, relies on Seibert et al CAPLUS abstract, AN 1998:366098 and particularly the sentence "The findings have led to the hypothesis that toxicities assocd. with NSAID therapies are due to inhibition of the non-regulated or constitutive form of COX (COX-1), whereas therapeutic benefit derives from inhibition of the inducible enzyme, COX-2", to take a position that as of the effective date of the filing there were no toxicities associated with administration of selective inhibitors of COX-2 and therefore it would be obvious

to administer them for their anti-inflammatory effect in respect to the diseases recited in the claims.

It is submitted that the position in the office action based on Seibert et al CAPLUS abstract, AN 1998:369098, is defective.

Firstly, the position the office action takes is defective because the Seibert abstract is not prior art, i.e., effective as of the effective date of the instant application. The relied on abstract is dated 1998 whereas the instant application claims benefit of U.S. Provisional Application No. 60/069,955, filed 12/17/97. While the relied on CAPLUS abstract is an interpretation of a 1997 article, it is an interpretation as of 1998. If the PTO wants to rely on the 1997 article rather than the 1998 interpretation, it needs to cite and provide a copy of the 1997 article.

Secondly, the position in the office action is defective even if the 1998 abstract is improperly given a 1997 date before 12/17/97, because the abstract is misinterpreted by the PTO. In this regard, see the declaration of Dr. Dannenberg submitted herewith which in paragraph 11 states:

> 11. What Seibert is saying to one skilled in the art is that while there has been a hypothesis (tentative assumption without proof) that gastrointestinal toxicities associated with NSAID therapy are due to inhibition of the non-regulated or constitutive form of COX (COX-1), we (G.D. Searle) now have proof that gastrointestinal toxicities associated with NSAID therapy are due to inhibition of COX-1 because we (G.D. Searle) have data that compounds that selectively inhibit COX-2 are anti-inflammatory without gastric toxicity.

Thus the toxicities referred to in the sentence relied on by the PTO, constitute gastrointestinal toxicities and not all toxicities associated with NSAIDs or liver toxicities, and the 1982 FDA

conclusion about liver toxicities for NSAIDs counts for selective inhibitors of COX-2, despite the CAPLUS abstract.

Thirdly, the position in the office action is defective even if the CAPLUS abstract is improperly given a 1997 data prior to 12/17/97 and is misinterpreted, because it relies on a hypothesis, that is a tentative assumption (by other than the authors of the CAPLUS abstract in this case) without supporting proof or evidence. It is submitted that an unobviousness position cannot be based on a hypothesis because a hypothesis cannot provide the reasonable expectation of success which is required (see In re O'Farrell, 7 U.S.P.Q. 2d. 1673 Fed. Cir. 1998)).

It is submitted that the above justifies allowance without further consideration.

However, it is pointed out that another error is in the Advisory Action in that it seems to take a position that hepatotoxicity would not be expected for selective inhibitors of COX-2 without showing of constitutive presence of COX-2 in liver. Please note that it was known at the time of the invention herein that COX-2 levels can increase during a disease process, that can have a healing effect; so administration of a selective inhibitor of COX-2 in these cases, can have a harmful effect. In this regard, see copies of Reuter, B.K., et al, J. Clin. Invest. 98, No. 9, 2076-2085 (11/96) and Mizuno, H., et al, Gastroenterology, 112, 387-397 (1997), copies attached. Reuter teaches that COX-2 increases after induction of colitis in a model therefor and selective inhibitor of cyclooxygenase-2 resulted in exacerbation of colitis indicating the selective inhibitor of COX-2 has a harmful effect in that case. Mizuno et al teaches that COX-2 mRNA levels were not detected under control conditions but were high during acute stages of gastric erosion and ulcers and that administration of NS-398, a selective inhibitor of COX-2, impaired the healing of ulcers leading to the conclusion that high levels of COX-2 mRNA and protein during the acute

stages of gastric mucosal lesions may be involved in the repair process (experiment in mice). In view of these substantially contemporaneous articles, one skilled in the art at the time of the effective filing date would not know whether COX-2 mRNA levels might increase in liver diseases for a healing effect and, in such case, administration of selective inhibitors of COX-2 would interfere with the healing effect--in other words, a scenario consistent with the 1982 FDA conclusion with respect to NSAIDs.

In any event, it is submitted that as of the effective date of the invention, the net benefit obtained by the invention in the case of treating the liver diseases of the claims, would not be obvious from the applied prior art.

Note also that the colitis (Reuter above) is an autoimmune disease--so the applied Gregory reference cannot even be generalized to all autoimmune diseases.

It is submitted that in view of the above, Claims 3-5 and 17 are unobvious over the applied prior art and therefore patentable.

It is submitted that since Claim 7 is conformed to Claim 3 in respect to disorders treated, Claims 7 and 9-11 as amended should also be patentable.

Entry of the amendments made herein and allowance of remaining Claims 3-5, 7, 9-11 and 17, is requested.

Respectfully submitted,

JONES, TULLAR & COOPER, P.C.

By: _____
Eric S. Spector
Reg. No. 22,495

JONES, TULLAR & COOPER, P.C.
P.O. Box 2266 Eads Station
Arlington, Virginia 22202
703-415-1500

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